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Three dimensional graphene transistor for ultra-sensitive pH sensing directly in biological media

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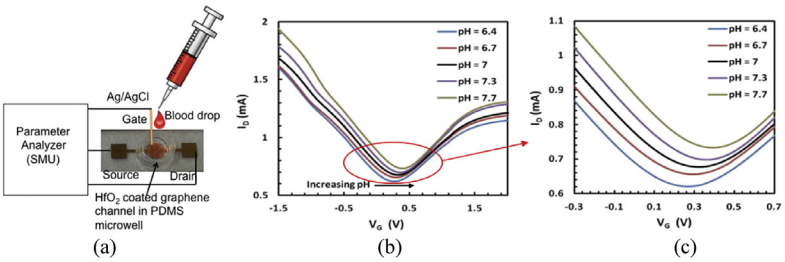
HIGHLIGHTS

- A three-dimensional graphene transistor for pH sensing is presented.
- It shows sensitivity of 71 ± 7 mV/pH even in high ionic strength media.
- High sensitivity attributed to 3D foam structure and all-around liquid gating.
- Enables real-time pH sensing in biological media without need of desaltation.

GRAPHICAL ABSTRACT



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ABSTRACT

In this work, pH sensing directly in biological media using three dimensional liquid gated graphene transistors is presented. The sensor is made of suspended network of graphene coated all around with thin layer of hafnium oxide (HfO_2), showing high sensitivity and sensing beyond the Debye-screening limit. The performance of the pH sensor is validated by measuring the pH of isotonic buffered, Dulbecco's phosphate buffered saline (DPBS) solution, and of blood serum derived from Sprague-Dawley rat. The pH sensor shows high sensitivity of 71 ± 7 mV/pH even in high ionic strength media with molarities as high as 289 ± 1 mM. High sensitivity of this device is owing to suspension of three dimensional graphene in electrolyte which provides all around liquid gating of graphene, leading to higher electrostatic coupling efficiency of electrolyte to the channel and higher gating control of transistor channel by ions in the electrolyte. Coating graphene with hafnium oxide film (HfO_2) provides binding sites for hydrogen ions, which results in higher sensitivity and sensing beyond the Debye-screening limit. The 3D graphene transistor offers the possibility of real-time pH measurement in biological media without the need for desaltation or sample preparation.

1. Introduction

Graphene has attracted a lot of attention in recent years for various electronic [1,2], sensing and bioelectronics [3–7] applications due to its high carrier mobility, high carrier concentration, biocompatibility, atomic thickness, electrochemical stability and mechanical reliability [8]. Many different biomolecules have been sensed using liquid-gated graphene devices where a solid-state dielectric is replaced by electrolytic double layer capacitance formed at the liquid-graphene interface [9,10]. Such configuration enables direct sensing in the liquid environment. Due to atomic thickness of graphene, its carrier density is very sensitive to the charge species in environment which enables charge-based detection of charged molecules and ions [10–12]. Using liquid

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gated graphene FETs for pH sensing, has been reported in literature, however reported pH sensing performance has not been consistent and sensitivities vary widely from 17 to 99 mV/pH [10,13–16]. Recently, it has been shown that a perfect defect-free graphene transistor is in fact not sensitive to the ions in the environment and the pH sensing may be mediated by the existence of defects and dangling bonds on the graphene surface and edges, and leakage current through bare source and drain gold contacts [16].

Another challenge in charge-detection based sensing of pH, especially for biological applications is the limited dynamic range due to charge screening in high ionic strength biological medium. Presence of electrical double layer at graphene/electrolyte interface results in exponential drop-off in the potential, away from the graphene/electrolyte interface. This effect is captured by the characteristic length known as Debye length beyond which the electrostatic effect of ions on the graphene channel is minimal. Debye length is defined as [10]

$$\lambda_D = \sqrt{\frac{\varepsilon kT}{e^2 \sum_i Z_i^2 n_{i0}}} \tag{1}$$

where ε is permittivity, K is the Boltzmann's constant, T is temperature, e is electron charge and Z_i is charge of the species i and n_{i0} is the concentration (number per volume) of the species i under equilibrium neutrality. At a constant temperature, Debye length just depends on the permittivity and ionic strength of the electrolyte. As an example, in a 100 mM aqueous electrolyte at room temperature, the Debye length is only about 1.3 nm, beyond which the charge carriers in the bulk will not have effect on the channel potential. In most biological medium, ionic concentration is higher than 100 mM. The osmolality of extracellular fluids and human blood serum is between 277 and 305 mOsmol/Kg, which correspond to 270–297.4 mM [17],; and Debye length in such high concentration medium will be even smaller. Therefore to be able to perform charge-detection based sensing of charged molecules and ions in biological samples, such as blood serum, urine and extracellular fluids, one needs to perform desaltation of the sample to reduce the overall ionic strength [18]. Sensing pH using graphene has not been reported in medium with concentration more than 100 mM due to such charge screening effect [13–16]. This limits the practical use of current graphene based sensors in real time monitoring of pH and other ions directly in the blood and biological fluids, which can be extremely useful especially in emergency medical care. For example, it is known that if arterial blood pH falls below 7.37 (normal range is 7.37–7.42), acidosis occurs [19]. Severe acidosis can lead to shock and death [20]. Therefore real time monitoring of pH of blood serum can be very valuable.

It has been shown that by adding oxide on graphene, the OH groups at the surface of oxide in contact with electrolyte can be protonated or deprotonated based on the pH of the solution and oxide surface composition [21–24]. In this case, the sensitivity of the device is not dependent on the electrolyte concentration [25]. Sensing pH using graphene-based liquid-gated field effect transistor (FET) with aluminum oxide dielectric acting as an ion sensitive layer has been reported [16]. It is shown that by growing less than 2 nm of Al_2O_3 using atomic layer deposition (ALD) at low temperature, the sensitivity of the sensor increases from 6 mV/pH to 17 ± 2 mV/pH[16]. In another work, the sensitivity of 40–50 mV/pH was achieved by adding high quality of aluminum oxide on the graphene [22]. The low sensitivity of earlier work is attributed to the poor quality of the oxide grown on graphene, due to low temperature growth process and low thickness of oxide (less than 2 nm). The sensitivity of such devices also depends on the type of oxide used as a sensing surface. It has been shown that using hafnium oxide, HfO_2, provides higher pH sensitivity of FET up to 59 mV/pH[26].

The pH sensitivity of conventional FETs and ISFETs is theoretically obtained using Nernst equation. Based on this equation the maximum sensitivity in such devices to pH is limited to 59 mV/pH, which comes from the relation between changes of electrostatic potential at the insulator-electrolyte interface, φ_0, with change of bulk electrolyte pH, pH_B, given by Ref. [25]

$$\frac{\partial \varphi_0}{\partial pH_B} = -2.3 \frac{kT}{e} \alpha \tag{2}$$

$$\alpha = \frac{1}{\left(\frac{2.3kTC_{dif}}{e^2 \beta_{int}}\right) + 1} \tag{3}$$

where α is dimensionless sensitivity parameter, C_{dif} is differential capacitance, β_{int} is intrinsic buffer capacity, k is Boltzmann constant, T is temperature, and e is electron charge. The sensitivity parameter is the function of differential capacitance and buffer capacity, which depends on the density of sensing sites on the surface and the ions in the sensing liquid [25]. As mentioned earlier, the maximum value of pH sensitivity given by equation (2) is 59 mV/pH at room temperature, known as Nernst limit. But one should notice that to derive Nernst equation, the oxide/electrolyte interface is modeled using either Hg/electrolyte or AgI/electrolyte interface so this equation is not valid at the oxide/electrolyte surface where variation of charge density with electrostatic potential, φ_0, is very different than Hg/electrolyte and AgI/electrolyte interfaces and in most of the oxides the surface charge density and differential capacities are higher than those in Hg and AgI [25–28]. It has been shown that sensitivity of the field effect transistors can be tuned by using different gate oxide materials and different configuration of transistor [22,23,29]. The pH sensitivity reported in dual gated FETs is considerably higher than Nernst limit [30,31]. The second gate in dual gated FETs enables compensation of the change in current induced by the first gate in response to pH which results in an effective amplification of the sensitivity. The super sensitivity of porous gate ISFET has also been reported where the effect was attributed to the 3D structure of the gate, results in the effective increase in the adsorption surface area and increased buffer capacity [32].

In this work, a three-dimensional suspended graphene is used as the channel of a liquid gated transistor. Graphene is coated with 20 nm hafnium oxide using atomic layer deposition (ALD) which acts as a pH sensing surface. The three-dimensional nature of this oxide-coated graphene foam results in a considerably larger sensing surface area. Moreover, the suspended structure of the liquid gated FET enables ions to accumulate all around, on exposed surfaces, resulting in significant improvement in liquid gate/channel coupling efficiency [33]. These effects have resulted in the proposed graphene transistor device to demonstrate a pH sensitivity of 71 ± 7 mV/pH, with the advantages of biocompatibility, potential flexibility and sensitivity in biological media with high ionic concentration.

2. Methods

The fabrication process flow of pH sensor is shown in Fig. 1. Process begins with placing CVD grown graphene (Graphene Supermarket Inc. USA) in ferric chloride solution ($FeCl_3$, 0.06 M) to etch away copper and then rinsing it with sufficient amount of deionized water (DI water) to remove the residue left over from the etching process. Titanium and gold were deposited through

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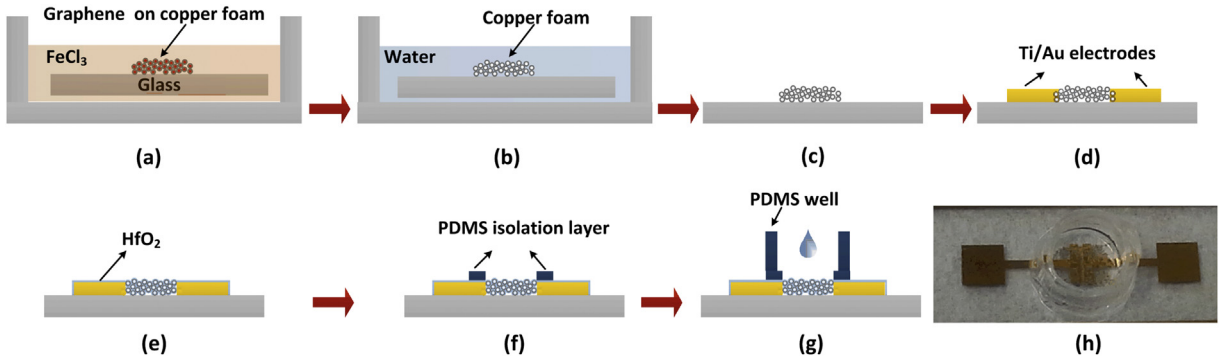

Fig. 1. Cross sectional view of the sensor fabrication process. (a) CVD grown graphene on copper foam is placed in $FeCl_3$. (b) After etching away copper, graphene is rinsed with DI water. (c) Graphene foam is dried. (d) Ti/Au is deposited through shadow mask to form source and drain connections. (e) HfO_2 is grown on the device. (f) Contacts area close to the channel is covered with PDMS protective layer. (g) PDMS well is fabricated and attached to the device. (h) Photo of the fabricated device with PDMS well.

shadow mask using DC magnetron sputtering (NSC 3000) with the thickness of 30 nm and 220 nm respectively to form source and drain contacts. The length and width of transistor were 600 μm and 5 mm, respectively. In the next step, 20 nm of HfO_2 was deposited using atomic layer deposition (Savannah ALD, Cambridge Nano-Tech) all over the device. Then an additional thin layer of PDMS (Polydimethylsiloxane) was added as a protective layer to prevent any direct physical contact between gold (source and drain contacts) and electrolyte thus minimizing leakage current. A well is made around the channel using PDMS and bonded to the device to prevent spreading of the electrolyte on the device. Dulbecco phosphate buffered saline (DPBS) (calcium chloride, $CaCl_2$, 1 gL^{-1}, magnesium chloride, $MgCl_2 \cdot 6H_2O$, 1 gL^{-1}, potassium chloride, KCl, 2 gL^{-1}, potassium phosphate monobasic, KH_2PO_4, 2 gL^{-1}, sodium chloride, NaCl, 80 gL^{-1}, sodium phosphate dibasic, $Na_2HPO_4 \cdot 7H_2O$, 21.6 gL^{-1}, water) [34] and blood serum of a male sprague-dawley rat were used to test the functionality of the pH sensor. Different DPBS (150 mM) based pH solutions with pH range from 3 to 9 were made by adding sodium hydroxide (NaOH) and Hydrochloric acid (HCl). The rat blood serum at four different pH values between 6.4 and 7.7 was used for testing the functionality of sensor directly in biological medium. The choice of the pH matches the known critical range of blood pH for diagnosis of acidosis. The initial pH of the serum extracted from the rat was measured to be 7.7. To provide blood serum with different pH, the blood was first extracted from a male Sprague-Dawley rat and added to a tube containing polymer gel for separating the serum. After separation of the serum, it was divided in to four parts. To simulate the blood acidosis, the pH of serum was adjusted at four different pH values from 6.4 to 7.7 by spiking it with appropriate amount of diluted hydrochloric acid, 0.03 M, through a nafion membrane. Since nafion is permeable only to the protons in the solution, we could simulate acidosis of blood by spiking the blood with hydrogen ions in HCl. The serum was stirred using a magnetic stirrer continuously to distribute the hydrogen ions that penetrated through the membrane evenly in the serum; the process was monitored using a pH meter. Once the pH of serum reached the desired value, it was used as a test sample.

3. Results and discussions

The channel of the presented transistor is made of CVD grown graphene on the copper foam. The SEM image of graphene grown on copper foam is shown in Fig. 2. After etching away the copper, graphene collapses but still maintains it's initial three dimensional structure (see Fig. 2(c)) [35]. Our previous study indicates that the graphene foam, is made of few layers of graphene [36]. As mentioned earlier, hafnium oxide as a sensing surface with the thickness of 20 nm was grown on the graphene after forming contacts. Due to the sp2 crystalline structure of graphene, hydrophobicity and lack of dangling bonds, growth of HfO_2 on graphene using ALD is challenging. Basically, the growth of HfO_2 on graphene starts at defects or boundaries of bilayer graphene islands, which usually form during the growth of monolayer graphene on copper and act as nucleation sites. It continues with formation of islands of oxide, grow in size and at a sufficient thickness merge with other islands and form a continuous layer [36]. To investigate the quality and continuity of the HfO_2 grown on graphene, X-ray photoelectron spectroscopy (XPS) of HfO_2 with the thickness of 20 nm grown on the graphene before etching away copper was performed at several random spots. The X-ray spot diameter was set to be 200 μm. Considering the fact that, the XPS only provides surface information and X-ray in XPS penetrates only 10–20 nm in the investigated layer and also that the thickness of the grown HfO_2 on graphene was 20 nm, one can correlate absence of copper peaks to deduce a presence of continuous layer of oxide at the top of the graphene. Fig. 3(a) shows the XPS results. As seen, all of the related peaks of HfO_2 exist in XPS spectrum. The C1s peak reveals the existence of carbon in the oxide layer, attributed to the organic residue from precursor decomposition during growth [37]. Fig. 3(b) shows high-resolution XPS spectra in the copper binding energy range, which shows absence of the copper peak, confirming the continuity of the HfO_2 films on the graphene. Sensing was performed in ambient environment at atmospheric pressure and room temperature. The leakage current was measured to be at least three orders of magnitude lower than drain to source current. Fig. 4(a) shows the transfer characteristics of the transistor gated with different DPBS based pH solutions with the pH values between 3 and 9. DPBS is a typical isotonic solution with molarity of about 150 mM, widely used for biological applications. With increasing pH of solution the Dirac point shifts towards more positive voltages. This behavior can be explained using site binding model [24], which depending on the pH of the electrolyte, oxide surface composition and hydrophilicity, the OH groups on the surface of oxide can protonate to form OH_2^+, remain neutral, or deprotonate to form O^{-16}. When pH of solution is acidic, OH groups protonate and as a result Dirac point shifts toward more negative voltages and when pH of solution is basic, OH groups deprotonate and the Dirac point shifts toward more positive voltages. Fig. 4(b) shows that the shift in Dirac point voltage of the device with pH change is linear. The error bars represent the variation of voltage shift for four devices fabricated and tested under the same conditions. The sensitivity of 71 ± 7 mV/pH was deduced for these sensors, which is greater than the Nernst limit. As explained earlier, the higher sensitivity is attributed to the larger sensing surface area and the high density of binding sites on

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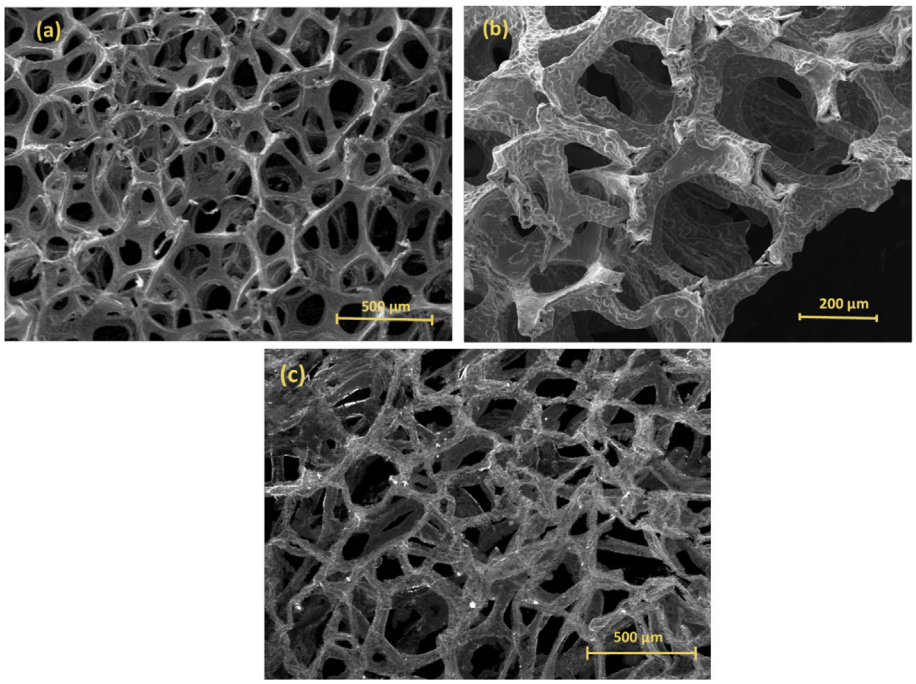

Fig. 2. SEM image of the graphene foam; (a) few layers graphene grown on copper foam; (b) graphene foam coated with 20 nm of HfO_2; (c) the SEM image of graphene foam after etching the copper.

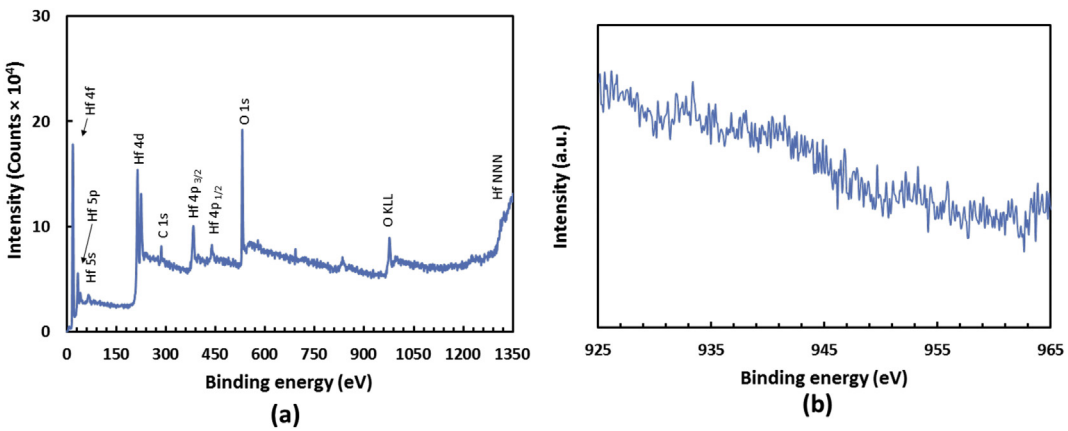

Fig. 3. XPS of hafnium oxide on graphene foam; (a) The XPS of HfO_2 with 20 nm thickness on the graphene before etching away the copper foam; (b) high resolution XPS spectra in copper binding energy range.

HfO_2. The resultant high charge accumulation on the surface and the all-around liquid gating of the transistor results in higher gate channel coupling efficiency which causes large Dirac shift in graphene transistor with small changes in pH. It should be noted here that the role of electrolytic double layer capacitance and the oxide capacitance in the Id-Vg shift is not as prominent as the quantum capacitance, which is in series with the other two; the increased sensitivity is primarily due to increased buffer capacity from large sensing surface area. Proposed device can perform sensing in higher ionic strength electrolyte background, which is typically known to be challenging for ISFETs [13,14,22,38]. Coating 3D graphene with HfO_2 as a sensing surface provides site binding for hydrogen ions in electrolyte and contribute to the sensing beyond Debye length. In fact, binding ions to the surface of HfO_2 transduces the charge accumulation to change in the conductivity of graphene. Also all around coating of the graphene with HfO_2 as a high K dielectric as well as electrolyte, provides higher control of the gate and consequently higher sensitivity of the device. In this device gate leakage current was measured to be three orders of magnitude lower than drain current as shown in Fig. 4(c). The real time monitoring of the pH was demonstrated and result is shown in Fig. 4(d). In this experiment, gate to source voltage was fixed at −0.5 V and drain to source voltage was set at 0.5 V. The solutions with different pH from 9 to 3 and then 3 to 9 were added at the top of the channel of transistor at 240-s intervals. The change in the drain current was then recorded for different pH solutions as a function of time. The result is consistent with the change in transfer characteristics of the transistor in the hole conduction regime (at $V_G = -0.5$ V) for different pH of electrolyte. Results show good reversibility for sensing pH between 3 and 9 using the presented device.

To investigate the functionality of the sensor in body fluids,

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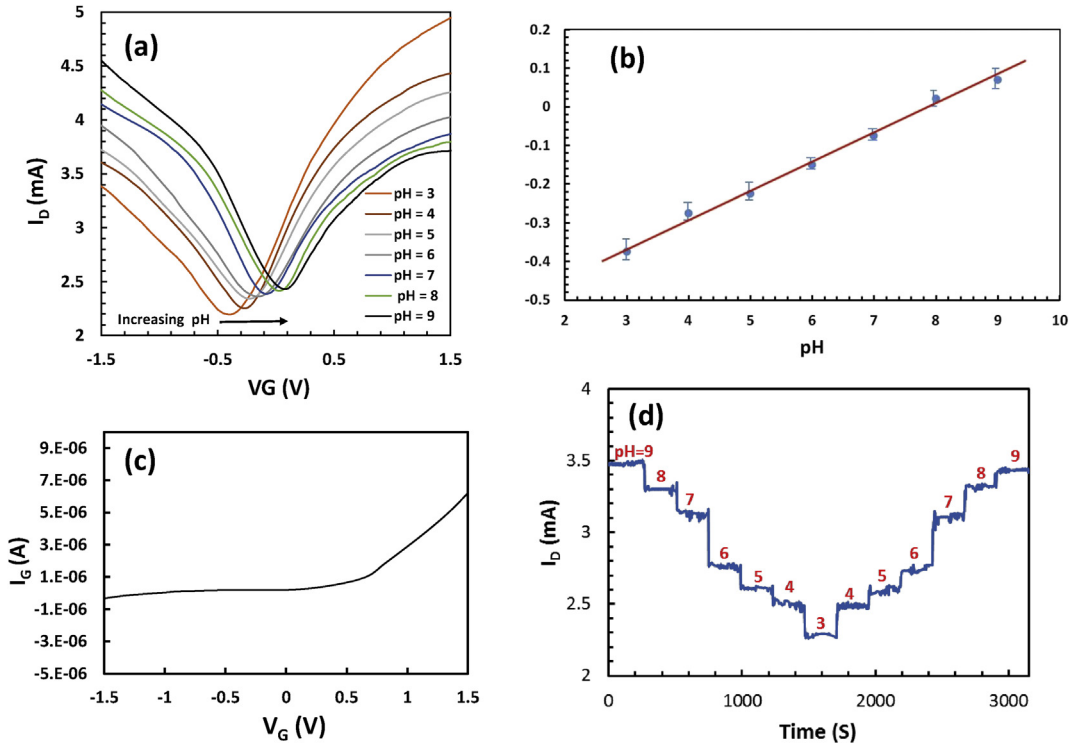

Fig. 4. Sensing results and sensor characterization; (a) transfer characteristics of transistor for different pH of DPBS; (b) shift of gate voltage at Dirac point at different pH solutions; (c) Gate leakage current of transistor at $V_d = 0.5$ V, pH = 5; (d) the real time monitoring of the pH with changing of the pH from 9 to 3 and then from 3 to 9.

blood serum of a rat (296 ± 1 mOsm/kg) at four different pH values from 6.4 to 7.7 was used. Rat blood serum with the pH of 7 first was added in the well. After measurement the serum was removed and measurement was continued with adding serum with pH of 7.3 and 7.7. Then the device was washed with deionized water and tested using serum with pH of 6.7 and 6.4 respectively. Results of sensing pH of the serum are shown in Fig. 5. As seen, the Dirac point shifts clearly toward more positive voltages with increasing pH from 6.4 to 7.7. The sensitivity of the device was not affected by the high ionic strength of the background electrolyte of around 289 mM in the rat blood serum compared to 150 mM in DPBS, indicating the ability of the sensor to work directly in biological medium without the need for desaltation or sample preparation. One should notice that the background charged molecules in the blood plasma would also be adsorbed on to HfO_2 layer and thus influence the pH measurement. The sensor should therefore be characterized for all the possible variation in the blood background to parameterize this dependence. This is beyond the scope of this paper and could be focus of future work.

4Conclusions

In conclusion, a highly sensitive pH sensor is demonstrated based on 3D liquid gated graphene transistor. The channel of this device consists of suspended three dimensional graphene network covered all around with HfO_2 layer as a sensing surface. Device shows high pH sensitivity of 71 ± 7 mV/pH exceeding the Nernst limit even in high ionic strength media. The superior performance of the device is attributed to the suspended configuration and the high surface area of the three dimensional graphene which

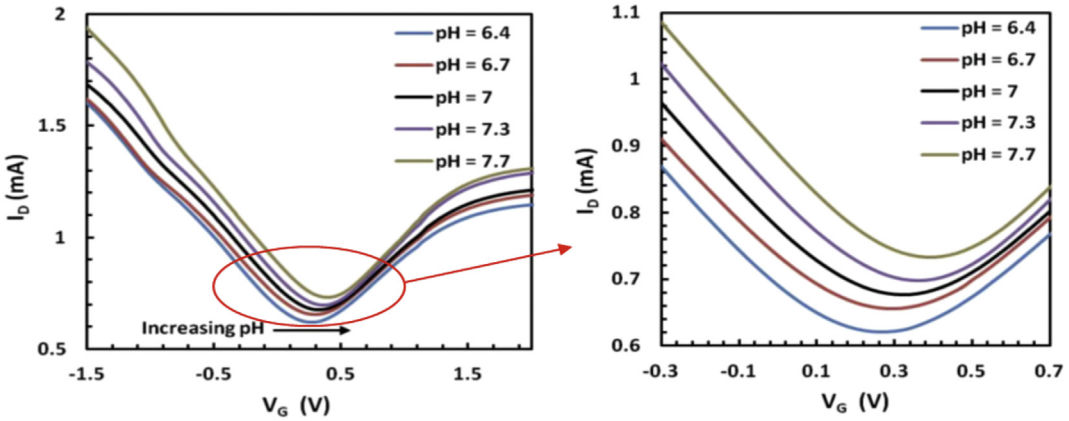

Fig. 5. Transfer characteristics of the transistor for blood serum at different pH values.

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provides all around electrostatic gate control. This results in enhancement of coupling efficiency between ions in the electrolyte and the graphene channel. High surface area of HfO_2, coated all around graphene provides binding sites for hydrogen ions and enables high sensitivity and sensing beyond the Debye-screening limit in high ionic strength media such as DPBS and blood serum and has the potential to be used for the real time monitoring of pH directly in such biological environment, with applications in medicine and life sciences. One application is that of monitoring blood pH in emergency medical care for real-time monitoring of acidosis in patients, and another application is that monitoring in-vitro pH of cells and tissue in tissue engineering and drug screening applications.

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